REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 21-58 were pending in this application when last examined. Claims 1-20 and 59 were previously cancelled. Claims 26-58 have been withdrawn as non-elected subject matter. Claims 21-25 have been examined on the merits and stand rejected. No claims have been allowed.

By way of the present amendment, claim 21 has been amended and new claim 60 (which depends on claim 21) has been added. Support for the amendment to claim 21 can be found in the disclosure, for example, at page 6, lines 1-22 and lines 19-22, and at page 25, lines 1-5. Support for new claim 60 can be found in the disclosure, for example, at page 6, line 15 and at page 25, lines 1-5. No new matter has been added.

Claims 21-58 and 60 are pending upon entry of this amendment. Applicants request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

II. Enablement Rejection

Claims 21-25 remain rejected under 35 USC §112, first paragraph, for lack of enablement for the reasons on pages 2-8 of

the Office Action. This rejection is respectfully traversed as applied to the amended claims. The arguments traversing this rejection set forth in the response filed July 22, 2009 are reiterated herein by reference.

First, starting with the second paragraph on page 3 of the Office Action, the Examiner argues that the specification is not enabling for the method of delivering/administering an agent capable of modulating NIK-SIVA to an individual to treat an immune disorder. The Examiner argues that the predictability of *in vivo* gene therapy methods for successfully delivering agents that would modulate the interaction between two intracellular proteins and thereby treat a disease is extremely low. According to the Examiner, no evidence has been presented demonstrating the effectiveness of this method of delivery to modulate any protein, let alone treat a disease. Applicants respectfully disagree for the reasons made of record in the last response.

Nonetheless, for the sole purpose of expediting prosecution and not to acquiesce to the Examiner's position, the claims have been amended in a manner believed to obviate this concern. In this regard, main claim 21, as amended, now requires decreasing NIK-SIVA formation and defines the agent as an antibody capable of binding to the amino acid sequence at amino acid coordinates 123-175 of SEQ ID NO: 3 (SIV1) or to the amino acid sequence at amino acid coordinates 58-110 of SEQ ID NO: 4

(SIV2), or a small interfering RNA molecule, or a ribozyme. As such, the amended claims no longer read on gene therapy. It is believed that the application fully enables methods of administering the recited agents to subjects in need thereof for therapeutic purposes, and in particular, to decrease NF-κB inducing kinase (NIK)-SIVA complex formation and to thereby treat an immune disorder.

Antibodies specific to the noted sequences are described in the application as capable of down-regulating a target gene product of the present invention, *i.e.*, NIK or SIVA down regulation (see the application at page 24, line 32, to page 25, line 5). These antibodies interfere with NIK-SIVA complex formation and thereby reduce NF-κB signaling (page 24, line 32, to page 25, line 5). Similarly, small interfering RNA and ribozymes are disclosed as being agents capable of down-regulating a target gene of the present invention (page 28, lines 27-28; pages 45-50 (Example 2), and page 32, lines 27-28).

In addition, the specification at pages 37-41 describes, in detail, the various methods and procedures for formulating dosages and pharmaceutical compositions and for delivery of such therapeutic agents to recipients for treatment purposes. It is again noted that the specification even discloses examples of such treatments, for instance, the "treatment of SLE-prone mice with a BLyS antagonist ameliorates disease progression

and enhances survival" and cites the reference Stohl (*Arthritis Res. Ther.* 5:136-138, (2003)). The specification describes how modulation of BLyS protein can effectively treat a disease condition.

Based on this guidance in the specification (and as corroborated by the references submitted with the last response), it is believed that the specification enables the skilled artisan to administer therapeutically effective amounts of the claimed agents to a subject for treatment purposes, and in particular, to decrease NF-κB inducing kinase (NIK)-SIVA complex formation and to thereby treat an immune disorder (*e.g.*, B-cells chronic lymphocytic leukemia (B-CLL)), wherein the agent is an antibody capable of binding to the amino acid sequence at amino acid coordinates 123-175 of SEQ ID NO: 3 (SIV1) or to the amino acid sequence at amino acid coordinates 58-110 of SEQ ID NO: 4 (SIV2), or a small interfering RNA molecule, or a ribozyme.

For these reasons, it is believed that the specification fully enables the claimed method of administration for treatment.

Second, at the top of page 3 of the Office Action, the Examiner argues that "the prior art does not show interaction between NIK and SIVA and a link between this interaction and any disease." On pages 4-5, the Examiner argues that the application and the prior art do not show interaction between NIK and SIVA

and a link between this interaction and any disease, and thus there is no evidence showing that modulating NIK-SIVA complex formation would constitute efficient treatment. The Examiner again argues that there is no nexus between NIK-SIVA interaction and a disease. Accordingly, the Examiner rejects the claims for an alleged lack of evidence that the modulation of NIK-SIVA complex formation has a therapeutic effect on an immune disorder. Applicants respectfully disagree for the reasons set forth in the last response and for the following reasons.

As disclosed in the application, NF-κB is a transcription factor that is active in inflammatory and immune cell responses (page 1, lines 15-21). In the application, it has been shown that NIK and SIVA impact the NF-κB pathway. In this regard, Example 1 (beginning on page 42) shows NIK and SIVA form a complex and, further, that co-expression of NIK and SIVA results in strong activation of NF-κB (pages 42-45). Specifically, when either SIVA1 or SIVA2 was expressed alone, only a slight activation of NF-κB was observed (page 45). In contrast, when NIK was co-expressed with either construct, an enhanced NF-κB activation was observed; an effect that was absent for overexpressed NIK aly mutant (page 45, lines 14-17 and Fig. 1e).

Also, in Example 2 (beginning on page 45), it is first shown that CD27 is involved in the activation of the NF-κB

pathway using the CD27 ligand, CD70 (pages 49-50). It is next shown that using a siRNA that blocks NIK synthesis, CD70 fails to activate the NF-κB pathway (page 50).

Based on such, it is respectfully submitted that the skilled artisan, upon reviewing the disclosure, and for instance, Example 2, would reasonably conclude that the lack of NIK necessarily results in a lack of NIK-SIVA complex formation and consequently an inability to activate the NF-κB pathway. As such, it is believed that the application demonstrates that NIK-SIVA complex formation is associated with the activation of the NF-κB pathway and that down-regulation of one member of this complex results in loss of signaling through this pathway. Thus, in contrast to the Examiner's arguments, the skilled artisan, upon reading the application and in view of the knowledge in the field, would find it plausible that agents that interfere with NIK activity and NIK-SIVA complex formation would necessarily interfere with the activation of the NF-κB and consequently interfere with diseases mediated by the NF-κB pathway.

Third, contrary to the argument that the application fails to provide any evidence of agents inhibiting NIK-SIVA interaction, the interaction between NIK and the amino acid coordinates 123-175 of SIVA1 (SEQ ID NO:3) or the amino acid coordinates 58-110 of SIVA2 (SEQ ID NO:4) is shown in the application. Specifically, Figure 1a shows that a strong

interaction is measured between the C-terminal portion of NIK and the C-terminal portion of SIVA, *i.e.*, the amino acid coordinates 123-175 of SIVA1 (SEQ ID NO:3) or the amino acid coordinates 58-110 of SIVA2 (SEQ ID NO:4) (page 8, lines 18-25, and Figure 1a).

Given this disclosure, the skilled artisan person would find it plausible that an antibody directed to the above mentioned regions would disrupt the interaction between NIK and SIVA. Nothing has been presented by the Examiner as to why this would not be true. As such, based on the description at page 8 and Fig 1a, the skilled artisan would find it plausible that an antibody directed to the above mentioned regions would disrupt the interaction between NIK and SIVA.

Thus, as discussed in the last response, the specification discusses in detail and establishes (see for example, the bottom of page 17 and at the top of page 18) that, in contrast to what was known, NIK does participate in the canonical NF-κB activating pathway, and that NIK also participates in activation of the alternative NF-κB activating pathway via CD70/CD27 signaling. Moreover, the specification discloses in detail how NIK inhibitory agents are useful to treat diseases which are caused or aggravated by NF-κB activation. The specification provides numerous examples of such immune disorders, which include: multiple myeloma (MM), acquired immunodeficiency syndrome (AIDs), Sjogren's syndrome (SS), B-

cells chronic lymphocytic leukemia (B-CLL), systemic lupus erythematosus, inflammatory colon disease, systemic inflammatory response syndrome (SIRS), multiple organ disinfection syndrome (MODS) and acute respiratory distress syndrome (ARDS). See, for instance, paragraph [0012] of the published application.

Further, as discussed in the last response, the specification does provide an example, at paragraph [0093], and demonstrates a link between NIK and the B lymphocyte stimulator (BLyS) protein, and the involvement of this protein in disease conditions, for example, multiple myeloma (MM). It explains that MM cells were shown to express BLyS receptors and BLyS, in turn, was shown to modulate proliferative capacity and survival of MM cells, and that the BLys protein was also found in the bone marrow of MM patients. The specification discloses that the BLys protein has been shown to be associated with a number of disease conditions: HIV; Sjogren's syndrome (SS); systemic lupus erythematosus (over-expression of BLyS in mice leads to a systemic-lupus-erythematosus-like (SLE-like) disease); and over-expression of BLyS is also common in human SLE. The specification also indicates that "treatment of SLE-prone mice with a BLyS antagonist ameliorates disease progression and enhances survival".

As discussed in the last response, this is but one example of how modulation of a protein can affect the NF-κB

activating pathway and treat a disease condition. It is believed that such could be extrapolated to the claimed method for treating the elected immune disorder of B-cells chronic lymphocytic leukemia (B-CLL). In this regard, the specification discloses that an effect of ByLS was demonstrated in B-cell chronic lymphocytic leukemia (B-CLL) and it indicates that the therapeutic application involves down-regulation of BLys signaling through NIK-dependent NF-κB pathway to overcome the described immune disorders. Thus, it is believed that the specification discloses down-regulating BLys signaling through NIK-dependent NF-κB pathway to treat immune disorders, such as B-cells chronic lymphocytic leukemia (B-CLL).

Accordingly, it is believed that such could be extrapolated to the claimed method for treating the elected immune disorder of B-cells chronic lymphocytic leukemia (B-CLL). Thus, it is believed that the specification establishes how modulating NIK-SIVA complex formation can regulate signaling through NIK-dependent NF-κB pathway to thereby treat an immune disorder.

Lastly, contrary to the Examiner's at the bottom of page 7 of the Office Action, the reference articles submitted with the last response do address the issue at hand, *i.e.*, a link between NIK-SIVA interaction and disease. Again, these references disclose and describe NIK and SIVA expression and

their interaction and its relationship to disease. It is believed that taken together they corroborate the link between NIK-SIVA complex formation and disease (B-CLL) and the treatment as set forth in the instant application.

For instance, the references support a link between NIK-SIVA formation to apoptosis and cell death and indirectly to cancer and B-CLL. In this regard, Everett et al. (*Am J Hematol.*, 2007 Jan, 82(1):23-30) discusses the cancerous phenotype in B-CLL and how it results from NF-kB activation through NIK containing complex. This paper describes that agents, e.g., curcumin, are capable of inhibiting NIK complex have potential therapeutic value against cancer, and in particular, B-CLL. Everett et al. examines whether a clinically achievable concentration of curcumin (1 microM) would augment the apoptotic effects of fludarabine, dexamethasone, vincristine or the PDE4 inhibitor rolipram in B-CLL cells from patients. They found that curcumin treatment reduced basal nuclear NF-kappaB levels and 1 microM curcumin augmented both vinca alkaloid and PDE4 inhibitor-induced apoptosis in B-CLL cells, which supports the idea that agents effecting NIK modulation, such as curcumin, may augment the efficacy of established or experimental therapies for B-CLL. This paper clearly supports the position in the application of a link between NIK-SIVA complex formation and disease, B-CLL.

Again, it is believed that such could be extrapolated to the claimed method of treatment.

Again, as argued in the last response, based on the previously submitted literature references, it seems that Curcumin causes inhibition of NF-kB and upregulation of SIVA at the same time and it is likely that the upregulated SIVA might be the agent inhibiting NF-kB through its down regulation of NIK. This is supported by the Song et al., Murph et al., and Fortin et al. references, also submitted with the response.

Applicants again respectfully submit that the specification as corroborated by these journal references effectively rebuts the argument questioning the link to disease and the feasibility of the claimed method of treatment.

Therefore, based on the guidance in the disclosure, as corroborated by the previously submitted references, Applicants respectfully submit that the specification enables one skilled in the art to practice the claimed method of treating an immune disorder (*e.g.*, B-cells chronic lymphocytic leukemia (B-CLL)) by administering a therapeutically effective amount of an agent to decrease NIK-SIVA complex formation, wherein said agent is (i) an antibody capable of binding to the amino acid sequence at amino acid coordinates 123-175 of SEQ ID NO: 3 (SIV1), (ii) an antibody capable of binding to the amino acid sequence at amino acid coordinates 58-110 of SEQ ID NO: 4 (SIV2), (iii) a small

interfering RNA molecule, or (iv) a ribozyme. It is believed that such could be done without undue experimentation based on the guidance in the disclosure and the knowledge in the field. For these reasons, withdrawal of the rejection is requested

III. Conclusion

Having addressed all the outstanding issues, the amendment is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance, and favorable action thereon is requested. If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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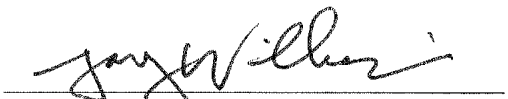
By 
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